DIAKONHJEMMET SYKEHUS

Self-reported fatigue in patients with rheumatoid arthritis:

Repeated cross-sectional analyses over a 15 year follow-up

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Objective. To estimate the prevalence and longitudinal development of fatigue in a Norwegian cohort of 238 patients with long-standing rheumatoid arthritis. Additionally; to examine cross-sectional association between fatigue and measures of disease activity, self-reported health status and damage in our cohort.

Methods. A cohort of 238 patients with rheumatoid arthritis has been followed since 1992. The prevalence of self-reported fatigue was determined and clinical laboratory and radiographic data used in the present study were collected at 5, 10 and 15 years after baseline. The longitudinal development of fatigue was investigated in the 10 most fatigued, and the 10 least fatigued patients, in groups defined on the basis of the results from 2007. Linear regression analyses were performed to identify variables strongly associated with fatigue at the different time-points. The variables included were divided into eight categories, each reflecting important aspects of RA. From the categories with a significant relationship to fatigue, the strongest predictive variable was included in a stepwise multiple regression.

Results. The prevalence of clinically relevant fatigue (VAS ≥ 20 mm) was 70.1 % in 1997, 79.1 % in 2002 and 80.0 % in 2007. High levels of fatigue (VAS ≥ 50) were present in 41.2 %, 39.6 % and 41.9 % at years 1997, 2002 and 2007, respectively. The longitudinal development of fatigue in the 10 most fatigued, defined by the VAS-scores from 2007, showed an increasing trend. Among the 10 least fatigued, also based on the data from 2007, the fatigue levels showed a more heterogeneous picture.

At years 5 and 15, the categories showing a significant relationship with fatigue in the linear regression analyses were disease activity, pain, physical function, psychosocial status and general health. A similar relationship was found at the 10 year follow-up, except that there was also significant correlations between fatigue and measures of damage. The final models from 1997, 2002 and 2007 explained 41.7 %, 46.9 % and 26.8 % of the variance of fatigue, respectively.

Conclusion. The prevalence of clinically important and high levels of fatigue remained stable in the course of the follow-ups in our cohort of patients with rheumatoid arthritis. Fatigue appears to be mainly linked to pain, general health and psychosocial status, and only to a lesser extent to disease activity.

Introduction

Rheumatoid arthritis is a chronic, inflammatory disorder, with a high impact on all aspects of health, as described in the definition presented by the World Health Organization in 1948. Part of this impact is constituted by fatigue, one of the many important symptoms of rheumatoid arthritis. It can occur as a prodromal symptom or as a precursor to increased arthritis disease activity [1].

A consensus definition of fatigue is not yet presented, but Piper [2] has defined chronic fatigue as something that "is perceived as unpleasant, unusual, abnormal or excessive whole-body tiredness, disproportionate to or unrelated to activity or exertion and present for more than one month. Chronic fatigue is constant or recurrent, it is not dispelled easily by sleep or rest and it can have profound negative impact on the person's quality of life."

In patients with RA, fatigue can be severe, and is besides pain the most troublesome symptom to handle [3-6]. In a Dutch study exploring patient`s experience of fatigue, almost half of the respondents attribute having a daily episode of fatigue with a greater impact on daily life than pain [4]. Patients from UK add to the description that fatigue is a frequent, extreme and multidimensional experience, with consequences that affect every aspect of life and lead to major disruption and distress [5]. In the elaboration of the preliminary Rheumatoid Arthritis Impact of Disease Score, patients from 10 different European countries ranked fatigue as the third most import domain to be included in the score [9].

Patients believe that RA fatigue is caused by inflammation, co-morbidity, age and disability, but frequently it occurs without a specific reason [3, 4]. It can be unexpected, sudden of onset and without a specific pattern, which makes it especially frustrating and difficult for the patients to handle. Patients describe their fatigue before the diagnosis of RA as explainable and spontaneously resolving, whilst fatigue after the diagnosis is far more complex [3, 7, 10].

Fatigue has been given a lot of attention by researchers, clinicians and patients during the last decades. Fatigue has proved to be an important outcome measure [7] that needs to be addressed by professionals in the same way as pain and disability [8].

The opinion of fatigue as a complex clinical feature is shared by a lot of rheumatologists and other health care professionals who work with chronic diseases. The exact causes, as well as the proper way to treat fatigue, are so far not entirely clear. Clinical measures strongly associated with fatigue may become important targets of treatment.

Both patient centered and disease centered variables were included in our analyses in order to elucidate whether fatigue is a symptom that is associated with soluble biomarkers and disease-

specific measures, or a sensation that needs to be addressed in a more holistic and personal perspective. The aim of this study is to determine the prevalence and longitudinal development of fatigue, and to identify the variables most strongly associated with self-reported fatigue in a cohort of individuals with RA.

Materials and methods

Patient sample

At baseline in 1992, patients aged 20-70 years with RA, according to the ACR 1987 criteria [11], of less then 4 years duration were identified from the registry of the Department of Rheumatology, Diakonhjemmet Hospital, and from the registry of Akershus County Department of Rheumatology. 326 patients were invited to join the study, 268 (82%) accepted, and 238 met the inclusion criteria. Criteria of entry and exclusion were those set by the EURIDISS project [12]. At baseline the mean age (SD) was 51.9 years (13.0), 73.5% were female and the mean disease duration was 2.3 years (1.1). 60.5% were anti CCP positive, 47.9% were IgM rheumatoid factor (RF) positive and 21% had extraarticular manifestations. 182 were re-examined after 5 yrs. Reasons for the loss of 56 patients to the 5 yr follow-up were reluctance to participate further (n = 39), moving out of the area (n = 5) and death (n = 12). It has been shown earlier that the patients completing the 5-yr follow-up were younger than the non-completers (p = 0.01), but they were comparable for all other demographic and disease-specific features [13]. 149 were examined again after 10 years. After 15 yrs, 108 patients participated, of whom 107 answered the questionnaires, whilst 75 declined to participate, and 56 patients were deceased.

Assessment methods

Collection of clinical, laboratory and radiographic data used in the present study were performed at 5, 10 and 15 years after baseline. The data included in our analyses were divided into eight different categories, as shown in *Tables 1, 2* and *3*.

Demographic variables

Demographic variables included age, sex, marital status and education. Marital status was

dichotomized into levels 0 and 1 (0 = not married, divorced, widow/widower, 1 = married, living together). Education were also divided into two categories (0 = no university college or university education/no more education after completing senior high school, 1 = university college or university education).

Measures of fatigue

Fatigue was measured using a double anchored VAS labeled at one end, "Fatigue is no problem," and on the other end, "Fatigue is a major problem." The question read, "Have you had problems with fatigue/tiredness in the past week?" The range of the scale is 0 - 100, where 100 represents major problems with fatigue and 0 means no fatigue at all [14]. The VAS fatigue is a simple generic instrument, measuring only one general dimension of the symptom [10, 14, 30]. It is sensitive to change, well correlated to clinical variables [15], and Hewlett et al. [26] have identified evidence of reasonable validation for it in a systematic review of 23 scales in use.

Measures of disease activity

Disease activity was assessed by the Disease Activity Score (DAS 28) [16], tender joint counts 28, swollen joint counts 28 and the Ritchie Articular index.

The Disease Activity Score comprises tender and swollen joint counts from a 28 joint count, erythrocyte sedimentation rate (1^{st} hour; ESR), and patients' assessment of disease activity by a visual analog scale for general health (VAS, 0-100 mm scale, where 0 = no disease activity, 100 = extreme disease activity). The 28 joint count is a reliable and valid measure for joint assessment. The examination needed is easy to perform, and it addresses the joints that are critically involved [17]. Prevoo et al [18] have found that the validity and reliability of traditional joint indices do not differ substantially, and thereby, because of their simplicity, the 28 joint indices are preferable. The tender and swollen joint counts were performed by one trained research nurse.

Biomarkers

Serum was frozen at each visit and later batch analyzed. The presence of IgM-RF was analyzed with the use of an enzyme-linked immunosorbent assay technique and World Health Organization standard reference for RF preparations [19, 20]. Patients with IgM-RF values of greater than or equal to 25 IU/ml were defined as RF-positive. IgG antibodies to cyclic citrullinated peptide (Anti-CCP) was also analyzed at each time. The analyses were performed using a second generation ELISA (INOVA Diagnostics®), and the results were considered positive above a cut-off value of 25/ml [21]. Anti-CCP is, as opposed to RF, a very sensitive measure in the making of the diagnosis of rheumatoid arthritis, and it has earlier been proved a strong predictor of disease course in early

rheumatoid arthritis [22].
Erythrocyte sedimentation rate (ESR) and CRP were also categorized as biological markers. Determination of the ESR and the CRP was carried out at the local laboratory at each of the follow-ups.

Damage

Radiographic damage was at the 5 and 10 year follow-ups scored according to the van der Heijde modification of the Sharp method. Sixteen joint areas were assessed for erosions (score 0-5) and 15 areas were assessed for joint space narrowing (score 0-4) in each hand, rendering a potential maximum total score for both hands of 280. Conventional radiographs are available at 5 years, while radiographs at 10 and 15 years were digitized. Joint radiographs that could not be read (due to lack of visible joints on the radiographs or due to prior joint replacement/arthorodesis surgery) were given the last available score (last observation carried forward) [20].
In 2007, joint damage was evaluated using the rheumatoid arthritis articular damage score (RAAD score). The RAAD score is based on a clinical examination of 35 large and small joints (score range 0-70), and has been shown to be a quick and feasible method for measuring long-term articular damage in large RA populations [23]. The examinations at the follow-ups were performed by a trained research nurse.

Pain VAS

Pain severity was assessed using a double anchored VAS labeled at one end, "No pain," and on the other end, "Unbearable pain." The question read, "How would you describe your regular pain during the past week?" The range of the scale is 0 - 100, where 100 equals worst imaginable pain and 0 being no pain at all.

The Stanford Health Assessment Questionnaire (HAQ)

The Stanford Health Assessment Questionnaire (HAQ) [14, 24], assessing functional status, was filled in by the patients themselves without any assistance. The questionnaire consists of 20 questions examining 8 dimensions of activities of daily living (dressing and grooming, getting up, eating, walking, hygiene, grip, reach and other activities). For each item, there is a four-level difficulty scale that is scored from 0 to 3, representing normal/no difficulty (0), some difficulty (1), much difficulty (2), and unable to do (3). The scores are averaged into an overall HAQ-DI score on a scale from zero (no disability) to three (completely disabled). The scale has 25 possible values (i.e. 0, 0.125, 0.250, 0.375...), and the higher the score, the more disable the patient is. The HAQ has been validated in Swedish, which is very similar to the Norwegian language.

The Short Form 36 Health Questionnaire

The SF36 [14, 25] was also completed by the patients themselves. This questionnaire is designed as a generic indicator of health status for use in population surveys and evaluative studies of health policy, and has only more recently been used to complement disease-specific measures in clinical trials. It consists of 36 questions, grouped into eight multi-item subscales measuring general health (5 items), physical functioning (10 items), role limitations due to physical health (4 items), bodily pain (2 items), vitality/energy/fatigue (4 items), social functioning (2 items), role limitations due to emotional problems (3 items) and mental health (5 items). Each scale is expressed with values from 0 to 100, where a high score indicates good health. The subscales included in our analyses are general health, physical functioning, bodily pain, social functioning and mental health. SF-36 vitality was excluded from our analyses because of its similarity to measures of fatigue [26].

Arthritis Impact Measurement Scale (AIMS)

The AIMS [13, 14] is a multidimensional index that measures the health status of individuals with arthritis. It was developed in 1980, and consists of seven demographic items and 55 health status items, assessing physical, emotional and social well-being. The items are divided into nine scales: mobility, physical activity, dexterity, household activities, activities of daily living, social activities, anxiety, depression, and pain. The scores for each individual scale are transformed into a 0-10 scale, on which 10 equals worst possible health. Also, the patients' global assessment of the impact of arthritis was assessed by one item from the AIMS on a scale from 0 to 10. AIMS was used in both 1997 and 2002, and we included the scales measuring pain, physical activity, mobility, social activity, anxiety, depression and impact in our analyses.

Arthritis Impact Measurement Scale 2 (AIMS2)

The AIMS2 [14] is an expanded and revised version of AIMS, and was used at the 15 year follow-up. It is a multidimensional disease specific instrument with 78 items capturing information in 12 areas of health (mobility level, walking and bending, hand and finger function, self-care tasks, arm function, household tasks, social activity, support from family and friends, pain, work, level of tension, mood). These 12 scales can be aggregated into five major dimensions, concerning physical functioning, social interaction, pain, work and affect. The score is ranged from 0 to 10, where 10 equals worst possible health. AIMS2 also includes a separate question that addresses the patients' priorities for improvement in health, as well as a question about the total impact of RA. A short form of AIMS2 has been validated in Norwegian. The AIMS and the AIMS2 were compared, and the most similar scales from each of the questionnaires concerning pain, physical function, social

function/mental health and general health/energy were included in our analyses. From AIMS2 we included pain, physical, social interaction, affect and impact.

The General Health Questionnaire (GHQ)

The General Health Questionnaire [27, 28] is a standard measure of psychological distress. It was originally developed as a screening tool to detect those likely to have or be at risk of developing psychiatric disorders. It consists of 28 items assessing social withdrawal, anxiety, depression and somatic symptoms. Each item is accompanied by four possible responses, ranging from 0 to 3, yielding a total GHQ score between 0 and 84. Jenkinson and Fitzpatrick [27] has proven the GHQ to be a suitable instrument in assessing the impact of illness upon patients' lives, both in severely disabling disorders such as rheumatoid arthritis and milder conditions. In the current study, all four dimensions of the GHQ were included.

Statistical analysis

The following analyses were performed using SPSS14. The prevalence of fatigue at the 5, 10 and 15 year follow-ups were calculated, after having defined clinically relevant fatigue to be VAS $\geq$ 20 mm, and high levels of fatigue to be VAS $\geq$ 50 mm [29]. The longitudinal developments of the 10 most and the 10 least fatigued patients, were visualized by continuous graphs over the previous 10 years, using SPSS14 and Microsoft Excel.

The independent variables included in the current study were entered into a scatterplot with fatigue, to check the relationship of fatigue to each of the variables, and in particular to see if there were any outliers who could contribute to a misleading result. Then, a linear regression analysis was performed for each of the independent variables, controlled for age and sex. The relationships between fatigue and level of education, and fatigue and marital status, were also investigated. The independent variables from each category showing the most significant correlation with fatigue, were then included in a stepwise multivariate regression analysis. In categories where two variables significantly correlated with fatigue shared the same level of significance, the variable with the highest R sq adjusted was included in further analyses. The stepwise multivariate regression analysis resulted in three final models from each time-point, including only variables with a significant contribution. All p-values equal to or less than 0.05 were considered statistically significant, and all tests were two-sided.

Numbers of respondents in each of the different categories are presented in brackets in *Tables 2, 3* and *4.* Percentage of data missing at the three follow-ups ranged from 0 % to 37 %

(SF36 mental and general health at the 15 year follow-up). The average of data missing at each follow up, were 4.8 %, 2.0 % and 7.9 % at the 5, 10 and 15 year follow-up, respectively. The total average of missing data at all three follow-ups was 4.9 %. Cases were excluded in order to achieve the same number of patients being tested in each category.

All of the included patients gave written consents before participation, and the study was approved by the regional ethics committee.

Results

Prevalence of fatigue

The prevalence of clinically relevant fatigue was present in 70.1 %, 79.1 % and 80.0 % of the patients, at the 5, 10 and 15 year follow-ups, respectively. High levels of fatigue were present in 41.2 %, 39.6 % and 41.9 %. The results are shown in *Table 1*.

Table 1. Prevalence of clinically relevant and high levels of fatigue

	Clinically relevant fatigue (VAS ≥ 20 mm)	**High levels of fatigue (VAS ≥ 50 mm)**
1997	70.1 %	41.2 %
2002	79.1 %	39.6 %
2007	80.0 %	41.9 %

Longitudinal development

The foregoing longitudinal development of fatigue in the 10 least (*Figure 1)*, and the 10 most fatigued (*Figure 2)*, based on the results from 2007, showed different patterns.

The 10 least fatigued. Most of the 10 patients with the lowest fatigue scores in 2007 had their highest scores in 2002. Three of these patients scored their own fatigue higher than 80 on the VAS at the 10 year follow-up. Three patients reported their highest score in 1997, two of them slightly below 70. All other patients scored their fatigue below 30 on the VAS at all three time-points.

The ten most fatigued. In the 10 with the highest fatigue scores in 2007, the values showed

an increasing trend from 1997 to 2007. Among the 10 most fatigued, 5 patients reported their lowest scores in 2002. Only one of these 5 patients scored his or her fatigue above 80, whilst three of the least fatigued reached a similar level. The tendency in both 1997 and 2007 was on the other hand quite the opposite. Apart from one outlier, all of the scores were above 40.

Figure 1. Longitudinal development among the 10 least fatigued. The X-axis represents the time of the three follow-ups, whilst the Y-axis represents levels of fatigue on a 100 mm VAS scale.

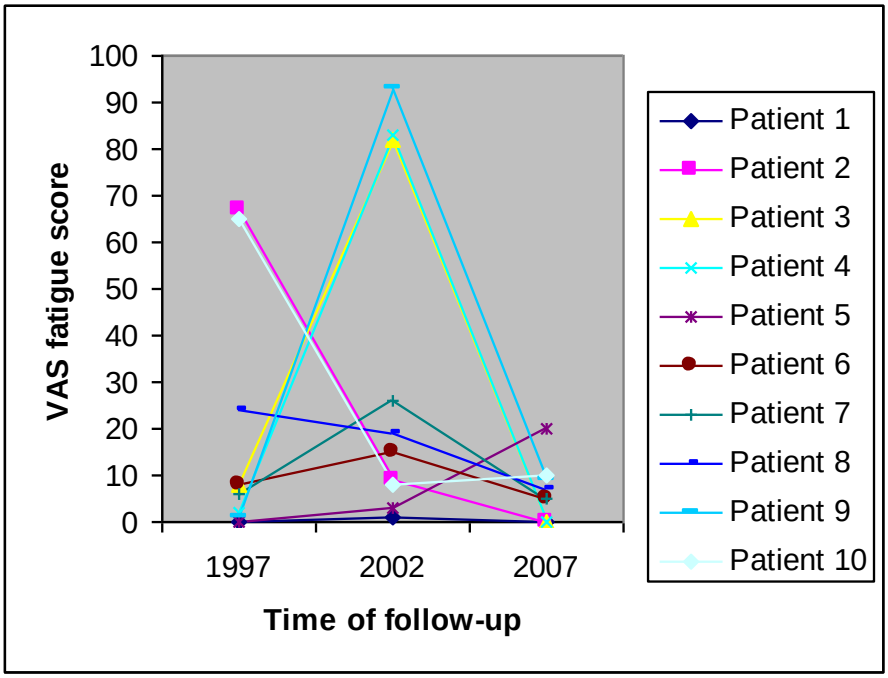
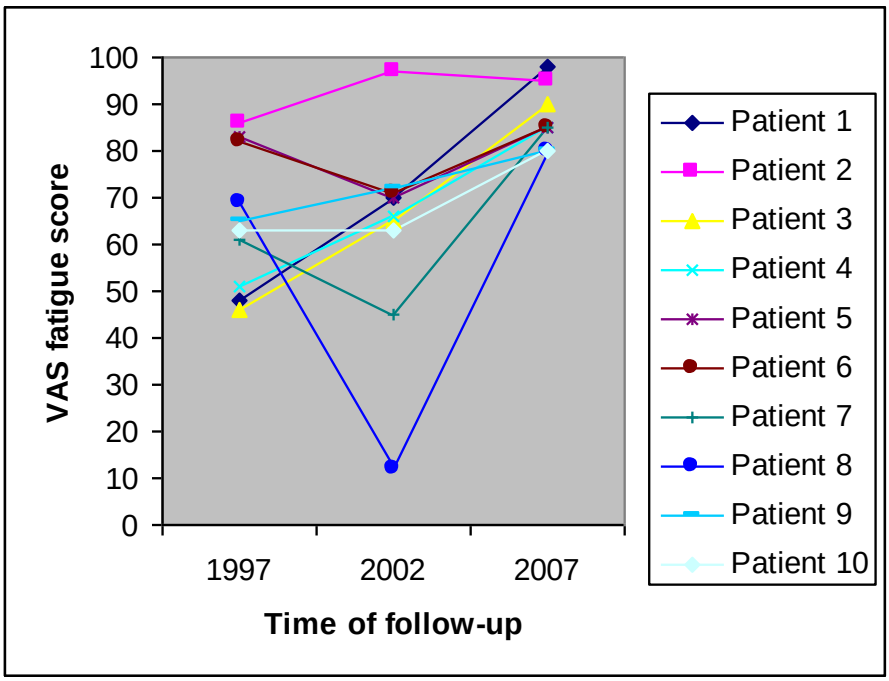


Figure 2. Longitudinal development among the 10 most fatigued. The X-axis represents the time of the three follow-ups, whilst the Y-axis represents levels of fatigue on a 100 mm VAS scale.



Univariate analyses

The results from the univariate analyses between fatigue and different variables, adjusted for age and sex, are presented in *Tables 2, 3* and *4.*

Demographic variables

Age and sex were not significantly correlated to fatigue at any time. In spite of this, they were included in all of the analyses, to exclude any confounding effects of age and sex on the final results.

Education and marital status, controlled for age and sex, did not show a significant association with fatigue, and was therefore not included in further analyses.

Disease activity

Among the three chosen measures of disease activity, the DAS 28 was the measure with the most significant relationship to fatigue at the 5 ($p = 0.01$) and 10 year ($p = 0.002$) follow-ups, explaining 4.0 % and the 7.0 % of the variance, respectively. Swollen joint count 28 was the only measure of disease activity with a significant relationship to fatigue at the 15 year follow-up ($p = 0.02$), explaining only 3.0 % of the variance.

Damage

Sharp scores were available from the 5 and 10 year follow-ups, but a significant association with fatigue was only found at the latter of these follow-ups ($p = 0.03$), explaining 4 % of the variance. RAAD scores were available at the 10 and 15 year follow-ups, but did not prove significant to fatigue at any of the time-points.

Biomarkers

No significant relationships were found between fatigue and any of the biological markers at any of the follow-ups.

Pain

All included measures of pain were significantly correlated to fatigue at all three follow-ups, sharing the same level of significance ($p < 0.00$) VAS pain was the measure with the strongest explanatory power towards fatigue at the 5 and 10 year follow-ups, explaining 22 % and 27 % of the variance, respectively. At the 15 year follow up, SF-36 pain was the measure with the highest explanatory power (24 %).

Physical function

HAQ was the measure of physical function showing the most significant relationship to fatigue ($p < 0.00$) at the 5 and 10 year follow-ups, explaining 17 % and 13 % of the variance, respectively. At the 15 year follow-up, SF-36 physical was the measure with the most significant relationship to fatigue ($p < 0.00$), explaining 18 % of the variance.

Psychosocial status

At the 5 and 15 year follow-up, SF-36 social function was the measure with the most significant relationship to fatigue ($p < 0.00$), explaining 23 % and 21 % of the variance, respectively. At the 10 year follow-up, SF-36 mental health was the measure most strongly related to fatigue ($p < 0.00$), explaining 29 % of the variance. Apart from AIMS social activity at the 5 and 10 year follow-ups and AIMS social interaction at the 15 year follow-up, all variables included in this category showed a significant association with fatigue at all three follow-ups.

General health

Among the measures of general health, GHQ somatic was the measure with the strongest association with fatigue ($p < 0.00$) at the 5 and 15 years follow-up, explaining 34 % and 18 % of the variance, respectively. At the 10 year follow-up, SF-36 general health was the measure with the most significant relationship to fatigue ($p < 0.00$), explaining 33 % of the variance. All variables included in this category showed a significant association with fatigue at all three follow-ups.

Table 2. 5 year follow-up. Results from the univariate analysis, with VAS fatigue (n=177) as the dependent variable (controlled for age and sex). Number of respondents are presented in brackets behind each variable.

	β	95% CI for β	p	Adjusted R square
Demographic variables				
Age (ctrl sex) (n=182)	0.11	-0.23 - 0.46	0.52	0,01
Sex (ctrl age) (n=182)	8.82	-1.13 - 18.76	0.08	0.01
Education (n=182)	-2.03	-11.84 - 7.78	0.68	0.003
Marital status (n=182)	5.35	-5.21 - 15.90	0.32	0.01
Disease activity				
DAS28 (n=172)	4.03	0.95 - 7.10	0.01	0.04
Swollen joint count 28 (n=179)	-0.07	-1.01 - 0.86	0.88	0.002
Tender joint count 28 (n=179)	0.74	0.02 - 1.45	0.04	0.03
Damage				
Sharp score (n=150)	-0.14	-0.32 - 0.03	0.11	0.02
Biomarkers				
Anti CCP (n=129)	0.01	-0.04 - 0.06	0.75	-0.01
IgM RF (n=129	-0.05	-0.10 - 0.01	0.11	0.02
CRP (n=179)	0.23	-0.24 - 0.70	0.33	0.01
SR (n=177)	0.01	-0.27 - 0.29	0.93	0.002
Pain				
VAS pain (n=178)	0.60	0.42 - 0.78	< 0.001	0.22
SF36 pain (n=177)	-0.39	-0.55 - -0.23	< 0.001	0.14
AIMS pain (n=175)	4.82	3.14 - 6.49	< 0.001	0.18
Physical function				
HAQ (n= 179)	17.89	11.41 - 24.38	< 0.001	0.17
SF36 physical function (n=178)	-0.44	-0.62 - -0.26	< 0.001	0.14
AIMS physical activity (n=179)	-0.28	-2.12 - 1.56	0.76	-0.003
AIMS mobility (n=174)	-0.81	-3.00 - 1.38	0.46	0.00
Psychosocial status				
SF36 mental health (n= 175)	-0.70	-0.94 - -0.47	< 0.001	0.19
SF36 social function (n= 176)	-0.52	-0.68 - -0.37	< 0.001	0.23
AIMS social activity (n=174)	-0.27	-2.90 - 2.36	0.84	-0.003
AIMS depression (n=174)	7.85	3.56 - 10.35	< 0.001	0.21
AIMS anxiety (n=173)	5.67	3.53 - 7.80	< 0.001	0.16
GHQ social (n=178)	4.03	2.79 - 5.27	< 0.001	0.21
GHQ depression (n=177)	3.11	2.05 - 4.16	< 0.001	0.19
GHQ anxiety (n=179)	2.63	1.76 - 3.50	< 0.001	0.19
General health				
SF36 general health (n=174)	-0.61	-0.79 - -0.42	< 0.001	0.22
AIMS impact (n=177)	5.29	3.35 - 7.23	< 0.001	0.16
GHQ somatic (n=179)	4.31	3.34 - 5.28	< 0.001	0.34

DAS28 = Disease Activity Score 28, VAS = Visual Analogue Scale, SF36 = Short Form 36 Health Questionnaire, AIMS = Arthritis Impact Measurement Scale, GHQ = General Health Questionnaire.

Table 3. 10 year follow-up. Results from the univariate analysis, with VAS fatigue (n=139) as the dependent variable (controlled for age and sex). Number of respondents are presented in brackets behind each variable.

	β	95% CI for β	p	Adjusted R square
Demographic variables				
Age (ctrl sex) (n=149)	0.05	-0.26 - 0.37	0.75	0,01
Sex (ctrl age) (n=149)	9.18	-0.43 - 18.79	0.06	0.01
Education (n=149)	3.20	-6.00 - 12.41	0.49	0.01
Marital status (n=149)	-0.49	-9.57 - 8.60	0.92	0.004
Disease activity				
DAS28 (n=147)	4.76	1.74 - 7.79	< 0.001 (0.002)	0.07
Swollen joint count 28 (n=148)	0.20	-0.59 - 0.99	0.61	0.01
Tender joint count 28 (n=148)	0.93	0.32 - 1.55	< 0.001 (0.003)	0.07
Damage				
Sharp score (n=147)	-0.13	-0.24 - -0.01	0.03	0.04
RAAD score (n=148)	-0.24	-0.74 - 0.26	0.35	0.01
Biomarkers				
Anti CCP (n=146)	-0.03	-0.07 - 0.01	0.16	0.02
IgM RF (n=146)	-0.03	-0.08 - 0.02	0.24	0.01
CRP (n=147)	0.15	-0.35 - 0.64	0.56	0.01
SR (n=148)	0.05	-0.30 - 0.41	0.77	0.01
Pain				
VAS pain (n=140)	0.54	0.39 - 0.70	< 0.001	0.27
SF36 pain (n=147)	-0.50	-0.65 - -0.34	< 0.001	0.23
AIMS pain (n=142)	5.30	3.73 - 6.88	< 0.001	0.26
Physical function				
HAQ (n=149)	13.86	7.64 - 20.07	< 0.001	0.13
SF36 physical function (n=147)	-0.35	-0.51 - -0.19	< 0.001	0.12
AIMS physical activity (n=148)	4.89	2.45 - 7.32	< 0.001	0.11
AIMS mobility (n=144)	2.35	0.48 - 4.21	0.01	0.05
Psychosocial status				
SF36 mental health (n=144)	-0.75	-0.96 - - 0.55	< 0.001	0.29 (0.289)
SF36 social function (n=147)	-0.54	-0.70 - - 0.38	< 0.001	0.26
AIMS social activity (n=144)	1.92	-0.50 - 4.34	0.12	0.02
AIMS depression (n=143)	7.42	5.00 - 9.83	< 0.001	0.22
AIMS anxiety (n=141)	6.90	5.00 - 8.81	< 0.001	0.29 (0.288)
GHQ social (n=146)	3.38	2.04 - 4.72	< 0.001	0.16
GHQ depression (n=146)	3.07	1.77 - 4.37	< 0.001	0.14
GHQ anxiety (n=147)	2.83	1.84 - 3.81	< 0.001	0.20
General health				
SF36 general health (n=142)	-0.65	-0.81 - - 0.49	< 0.001	0.33
AIMS impact (n=145)	5.51	3.91 - 7.10	< 0.001	0.26
GHQ somatic (n=148)	3.63	2.67 - 4.60	< 0.001	0.30

DAS28 = Disease Activity Score 28, RAAD score = Rheumatoid Athritis Articular Damage score, VAS = Visual Analogue Scale, SF36 = Short Form 36 Health Questionnaire, AIMS = Arthritis Impact Measurement Scale, GHQ = General Health Questionnaire.

Table 4. 15 year follow-up. Results from the univariate analysis, with VAS fatigue (n=105) as the dependent variable (controlled for age and sex). Number of respondents are presented in brackets behind each variable.

	β	95% CI for β	p	Adjusted R square
Demographic variables				
Age (n=108)	0.02	-0.02 - 0.07	0.28	-0.01
Sex (n=108)	0.39	-0.83 - 1.62	0.53	-0.01
Education (n=104)	-0.06	-1.14 - 1.02	0.91	-0.01
Marital status (n=104)	-0.21	-1.35 - 0.92	0.71	-0.01
Disease activity				
DAS28 (n=108)	0.42	-0.16 - 1.00	0.16	-0.003
Swollen joint count 28 (n=108)	0.19	0.03 - 0.35	0.02	0.03
Tender joint count 28 (n=108)	0.04	-0.10 - 0.19	0.54	-0.01
Damage				
RAAD score (n=107)	0.05	-0.02 - 0.11	0.14	0.01
Biomarkers				
Anti CCP (n=101)	0.003	-0.003 - 0.008	0.34	-0.01
IgM RF (n=101)	0.002	-0.001 - 0.005	0.12	0.01
CRP (n=107)	0.02	-0.01 - 0.06	0.14	0.01
SR (n=108)	-0.01	-0.05 - 0.03	0.71	-0.01
Pain				
VAS pain (n=105)	0.43	0.21 - 0.64	< 0.001	0.12
SF36 pain (n=86)	-0.05	-0.07 - -0.03	< 0.001	0.24
AIMS2 pain (n=105)	0.46	0.26 - 0.65	< 0.001	0.17
Physical function				
HAQ (n=107)	1.49	0.76 - 2.23	< 0.001	0.12
SF36 physical function (n=69)	-0.05	-0.07 - -0.02	< 0.001	0.18
AIMS physical (n=105)	0.56	0.22 - 0.90	< 0.001	0.08
Psychosocial status				
SF36 mental health (n=68)	-0.10	-0.18 - -0.02	0.02	0.06
SF36 social function (n=88)	-0.06	-0.08 - -0.03	< 0.001	0.21
AIMS2 affect (n=104)	0.79	0.45 - 1.12	< 0.001	0.17
AIMS2 social interaction (n=104)	0.28	-0.07 - 0.62	0.11	0.01
GHQ social (n=101)	0.28	0.06 - 0.50	0.01	0.05
GHQ anxiety (n=100)	0.35	0.20 - 0.50	< 0.001	0.18
GHQ depression (n=100)	0.32	0.13 - 0.51	< 0.001	0.09
General health				
SF36 general health (n=68)	-0.05	-0.08 - -0.02	< 0.001	0.13
AIMS impact (n=103)	0.82	0.27 - 1.37	< 0.001	0.07
GHQ somatic (n=100)	0.34	0.20 - 0.48	< 0.001	0.18

DAS28 = Disease Activity Score 28, RAAD score = Rheumatoid Athritis Articular Damage score, VAS = Visual Analogue Scale, SF36 = Short Form 36 Health Questionnaire, AIMS = Arthritis Impact Measurement Scale, GHQ = General Health Questionnaire.

Stepwise multivariate regression analyses

From each category, the variable with the lowest level of significance, and the highest R sq adjusted, given that the category contained measures with a significant relationship to fatigue (level 0.05), were included in a stepwise multiple regression. The collinearity was less than 0.7 between all of the entered variables. There were no confounding effects of any of the variables entered in the stepwise multivariate regression analysis, measured by checking the changing of the β-values during the analyses.

The final models from all three follow-ups are presented in *Tables 5*, *6* and *7*.

Table 5. Final model, 5 year follow-up, 1997

	β	95 % CI for β	p	Adjusted R square
Age	-0.02	-0.29 - 0.25	0.888	**0.417 = 41.7 %**
Sex	5.38	-2.29 - 13.06	0.168	
GHQ somatic	2.98	1.90 - 4.07	< 0.001	
SF36 social function	-0.18	-0.34 - -0.01	0.035	
VAS pain	0.30	0.12 - 0.48	0.001	

Table 6. Final model, 10 year follow-up, 2002

	β	95 % CI for β	p	Adjusted R square
Age	-0.18	-0.42 - 0.06	0.148	**0.469 = 46.9 %**
Sex	2.33	-5.00 - 9.67	0.530	
Das28	-3.54	-6.54 - -0.53	0.021	
VAS pain	0.32	0.14 - 0.50	0.001	
SF36 general health	-0.39	-0.60 - -0.17	< 0.001	
SF36 mental health	-0.46	-0.66 - -0.26	< 0.001	

Table 7. Final model, 15 year follow-up, 2007

	β	95 % CI for β	p	Adjusted R square
Age	0.02	-0.02 - 0.06	0.343	**0.268 = 26.8 %**
Sex	-0.07	-1.24 - 1.11	0.912	
SF36 social function	-0.03	-0.06 - 0.00	0.041	
SF36 bodily pain	-0.04	-0.06 - -0.01	0.007	

Discussion

Our most important findings were that the prevalence of fatigue remained stable in the course of the follow-ups, whilst the longitudinal development of fatigue among the 10 most and the 10 least fatigued patients showed a more heterogeneous picture. Regression analyses indicated that measures of disease activity, damage, pain, physical function, psychosocial status and general health were significantly associated with fatigue. In the final multivariate models, measures of pain,

psychosocial status, general health and disease activity were significant contributors to explaining fatigue.

The prevalence of clinically relevant and high levels of fatigue *(Table 1)* in the cohort remained more or less constant during the three follow-ups, a finding that is consistent with previous analyses, although they have not followed the levels of fatigue for more than one year [1, 8, 31]. Belza [1] argues that fatigue, because of its noted stability over time, seems to have more characteristics that would be associated with a trait, rather than a state.

Clinically relevant fatigue (VAS ≥ 20 mm) was present in 70-80 % of our cohort at all three follow-ups, whilst approximately 40 % experienced high levels of fatigue (VAS ≥ 50 mm). Pollard et al. [29] used the same levels of defining different degrees of fatigue, finding clinically relevant fatigue to be present in more than 80 % of a population of patients with RA, whilst high levels of fatigue were present in 50 %. Wolfe et al. [32], Belza et al. [33] and Mancuso et al. [31], using the VAS fatigue, the Multidimensional Assessment of Fatigue scale [26, 30] and the Fatigue Severity Scale [30], respectively, found similar frequencies of different levels of fatigue.

In interpreting the results from the current analyses of prevalence, one has to consider the possible confounding effects of the patients dropping out. Of the 238 patients included at baseline, only 108 attended the 15 year follow-up. During the 15 years of data collection 75 patients have declined to participate, and 56 patients are deceased. It is hard to determine whether the patients declining to participate or the patients deceased would have given different results, considering the heterogeneous continuous development of fatigue, as illustrated in *Figures 1 and 2*. It is possible that the patients declining to participate were too fatigued to participate any longer, or that the most fatigued were the ones that now are deceased. Levels of fatigue may on the other hand be completely unrelated to patients' willingness to participate.

To a certain extent, *Figures 1 and 2* gives the impression that the fatigued get more fatigued, whilst the least fatigued gets less fatigued. In our cross-sectional approach, it is not possible to determine whether these 20 patients reflect the true situation in our cohort. In order to examine this, mixed modeling would have been a suitable method. Thus, given the limitations of the current analyses, the graphs should merely be considered as illustrations on how levels of fatigue may develop over time in individual patients.

The clinical variables included in our analyses were not equally powerful in explaining variance in fatigue *(tables 1, 2 and 3).* In keeping with previous reports [1, 8, 29, 32-40], pain, general health and psychosocial factors were consistently the categories most strongly related to fatigue at all three follow-ups. We also found a significant correlation of fatigue to measures of physical function, disease activity and damage. With the exception of DAS-28 at the 10 year follow-up, none of these variables appeared to be significant predictors of fatigue in the multivariate regression

analyses.

The final models from each of the follow-ups differed regarding included variables as well as ability towards explaining fatigue (*Table 5, 6 and 7)*. The model as a whole at the 15 year follow-up explained only 26.8 % of the variance of fatigue, as opposed to 41.7 % and 46.9 % at the 5 and 10 year follow-ups, respectively. Such discrepancies between the models may indicate confounding effects of highly correlated variables, or that the association between fatigue and rheumatoid arthritis has become weaker during our follow-ups, or that we have not included all the relevant variables or simply that the disease has become milder [41]. In comparison with other studies evaluating fatigue at different disease durations, we did not find a similar pattern regarding the ability towards explaining fatigue. Huyser et al. [37] investigated correlates of fatigue in a population with a mean disease duration of 12.9 years, which resulted in a final model explaining 49 % of the variance of fatigue. Accordingly; Belza et al. [33] found different variables to explain 61 % of the variance of fatigue in patients with average disease duration of 18 years, predominantly females (75 %). These studies differ from the current regarding included variables, thus no rigid conclusions should be drawn based on the explanatory powers only. However, the findings of Huyser and Belza suggest that there is no evidence of fatigue loosing its association with rheumatoid arthritis in the course of the disease.

Concerning bivariate correlation in our final models, there will indubitably be some overlap in the explaining of fatigue. However, collinerarity diagnostics indicated no competing dependencies between any of the included variables. According to commonly used cut-off points for determining the presence of multicollinearity, acceptable levels of tolerance were set at above 0.4 [42], and corresponding levels of bivariate correlation at less than 0.7 [43]. In the current study, the lowest level of tolerance was 0.44, whilst the highest bivariate correlation was 0.64. Based on these results, we have not violated the multicollineratiry assumption.

In spite of the dissimilarities of the explanatory powers of the different final models, the strong explanatory power of pain was a common denominator through all three follow-ups. In the univariate analyses, pain explained more than 20 % of the variance of fatigue at all three time-points. Pain was the only variable included in the final model at all three follow-ups. The evidence of the strong association between pain and fatigue, irrespective of disease duration, is in accordance with many previous studies [1, 29, 31-40, 44, 45].

While demographic variables appear not to be significant factors in our correlation analyses, Belza et al. [33] and Hyuser et al. [37] found that female gender made a significant contribution to the explanation of fatigue. As distinct from the current study, Belza et al. and Huyser et al. used the Multidimensional Assessment of Fatigue scale and the Piper fatigue Self-Report scale (PFS) [30], respectively, to measure the degree of fatigue among the patients. Compared to the VAS fatigue,

these scales are more extensive, evaluating several dimensions of fatigue [15, 30], making different correlations more likely.

Also, biological markers (IgM RF, anti-CCP, CRP, ESR) were not significantly associated with fatigue, a finding that is consistent with results from several previous studies [1, 8, 32, 33, 37]. However, Davis et al. [46] has found heightened proinflammatory cytokine activity in RA patients at risk for fatigue symptoms.

Our study is limited by the relatively low number of patients included, and the repeated analyses do not compensate this fact. If the group had been larger, we may have identified biological markers or measures of disease activity as significant correlates of fatigue. Also, some variables previously shown to be significantly correlated to fatigue were not included in the current analyses. These variables are self-efficacy towards coping with RA and towards asking for help, learned helplessness, comorbid conditions and quality of sleep [1, 31, 32, 33, 34, 37]. We chose early to limit our investigation to certain dimensions of rheumatoid arthritis, and thus some important variables were excluded.

Another limitation of the current study is the use of a simple one-dimensional measure of fatigue. In addition, we did not have measures of fatigue from the baseline of the study.

One of the major problems in investigating characteristics of fatigue is that there is no "gold standard" definition, nor is there ever likely to be [30]. It is a big challenge to make sure that the patients have the same perception of fatigue as clinicians and researchers do. Some patients may apprehend it as tiredness or sleepiness rather than a more typical experience of fatigue. The use of extensive measures of fatigue may diminish these problems.

Cognitive behavioral therapy, aerobic training and some anti-rheumatic drugs have shown beneficial effects on fatigue [29, 46-55]. In spite of this, a qualitative study on how 29 patients with RA experience fatigue [4] showed that most patients did not discuss fatigue with clinicians explicitly. Not expecting support from health care professionals, they assume that they have to manage fatigue alone, as it is part of the disease. Additionally, they describe how they have to find their own management strategies by trial and error. These descriptions throw light on patient needs not yet met by health care professionals, thus a vast treatment potential lies in the fulfillment of these needs.

In conclusion, the current study has found fatigue to be a sensation that needs to be addressed in a holistic and personal perspective, yet some features of fatigue remain unexplained. Further studies are needed to find better correlates and improve treatment of RA related fatigue.

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